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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 09/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/987,456	ZAUDERER ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *84-131* is/are pending in the application.

4a) Of the above claim(s) *85-87,98,100-102,104-106 and 123-126* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *84,88-97,99,103,107-122 and 127-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/28;5/1;11/6;5/28*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Receipt is acknowledged of a Response to a Restriction Requirement, which was dated on May 28, 2004.

Status of the Claims

2. Claims 84-131 were pending in the present application. Applicants amended claims 109 and 112. No claims were added or canceled. Therefore, claims 84-131 are currently pending.

3. Applicant's response to the Restriction and/or Election of Species requirements in the 5/28/2004 Response is acknowledged (Applicant elected ***with traverse*** Group I, claims 84-122 and 127-131) and claims 123-126 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim.

4. Please note: Applicant's elected species (Subgroup 1 = HeLa cell; Subgroup 2 = capable of producing infectious particles; Subgroup 3 = IgG; Subgroups 4-5 are withdrawn (see below); Subgroup 6 = vaccinia virus which is not attenuated and is not deficient in D4R synthesis; Subgroup 7 = T7 phage promoter; Subgroup 8 = Promoter under control of T7 polymerase; Subgroup 9 = v7.5/tk virus genome; Subgroup 10 =

NotI; Subgroups 11-12 are withdrawn (see below); Subgroup 13 = ELISA, see rejections below. Applicants' elected species (Subgroup 14 = pVHE; Subgroup 15 = IgM –19 to –3 sequence) were not found in the art. Applicant is reminded of MPEP § 803.02 with respect to species elections:

> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. The prior art search, however, ***will not be extended unnecessarily to cover all nonelected species***. Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

5. Claims 85-87, 98, 100-102, 104-106 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species, the requirement having been traversed in Paper No. 6 (see below i.e., ***Response to Restriction and/or Election of Species***).

6. Therefore, claims 84, 88-97, 99, 103, 107-122 and 127-131 are examined on the merits in this action.

Response to Restriction and/or Election of Species

7. Applicant's election of Group I (i.e., claims 84-122 and 127-131) ***with traverse*** is acknowledged.

8. The traversal is on the ground(s) that **[1]** Groups I-V represent "related" subject matter (e.g., see paragraph bridging pages 21-22) and **[2]** *assuming arguendo* that Groups I-V represent distinct or independent invention, there would be no search burden on the Examiner and cite MPEP § 803 in support of this argument (e.g., see paragraph bridging pages 22-23 wherein Applicants argue that the search would "overlap substantially").

9. These arguments were fully considered but were not found persuasive. **[1]** First, the Examiner notes that mere presence of any alleged overlapping subject matter would not constitute a coextensive search because each Group would have to be searched to its full extent and not just to the extent of any overlapping subject matter, which would, as a practical matter, encompass non-overlapping subject matter and hence result in a non-coextensive search. **[2]** In addition, as stated in the Restriction Requirement dated April 28, 2004 (e.g., see paragraphs 3-9), these inventions (Groups I-V) have acquired a separate status in the art as shown by their different classification and/or divergent subject matter. The different methods and/or products would require completely different searches in both the patent and non-patent databases, and there is no expectation that the searches would be coextensive. Therefore, this does create an undue search burden for the Office.

10. Applicant's election of species in the 5/28/2004 Response ***with traverse*** is also acknowledged.

11. The election of species traversal is on the ground(s) that **[1]** there is no burden in searching method steps that are repeated (e.g., see 5/28/2004 Response, page 24, Subgroups 3-4; see also page 26, subgroups 11-12) and **[2]** there is no burden in searching the rest of the species either and cite MPEP § 806.04, § 806.05 and § 803 in support of this position (e.g., see page 28, especially the last paragraph wherein Applicants state, for example, that a "search of IgG as an immunoglobulin would provide useful information regarding other types of immunoglobulins, such as IgM" i.e., there is overlapping subject matter).

12. These arguments were fully considered but were not found persuasive. **[1]** The Examiner finds Applicants arguments persuasive and the species election with regard to subgroups 3-4 and 11-12 only is hereby ***withdrawn***. **[2]** The Examiner's position is that the species are distinct, each from the other, because the structures and modes of action of each of the species encompassed are different. They would also differ in their reactivity and/or mechanism and/or the products made. Therefore, the species have different issues regarding patentability and represent patentably distinct subject matter. Furthermore, the Examiner previously stated that should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be ***obvious variants*** or ***clearly admit*** on the record that this is the case. This has not been done.

However, it was also stated that upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as

provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

13. As a result, the restriction requirement and/or election of species is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

14. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98 (b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on the form PTO-892, they have not been considered.

15. The references listed on applicant's PTO-1449 form have been considered by the Examiner. A copy of the forms are attached to this Office Action (e.g., IDS filed 7/28/04, 5/1/03, 11/6/02 and 5/28/02).

Specification

16. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claims Rejections - 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 109 and 112 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed had possession of the claimed invention. This is a new matter rejection.

New claims 109 and 112 recite, "restriction site selected from the group consisting of NotI, ApaI, and a combination thereof." Applicants state that support can be found "throughout the specification", but do not provide any page number or line number. The Examiner does not find support for the "combination thereof" selection. If applicant believes this rejection is in error, applicant must disclose where in the specification support for this amendment can be found in accordance with MPEP 714.02.

18. Claims 84, 88-97, 99, 103, 107-122 and 127-131 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 USC 112, ¶ 1 "Written Description" Requirement, Federal

Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a written description rejection.

Applicants' claims encompass a broad genus. For example, the claimed invention outlines method steps for selecting polynucleotides, which encode an antigen-specific human immunoglobulin molecule, or antigen-specific fragment thereof. The scope of this claim includes an enormous number of methods using an enormous number of potential vaccinia viral genomes produced by an unspecified number of methods e.g., homologous recombination, direct ligation, etc. Consequently, the nature of the invention cannot be fully determined. Although the specification discloses examples of "tri-molecular combination" using "two" non-overlapping fragments of the cleaved v7.5/tk or vEL/tk virus genomes produced using NotI/ApaI restriction enzymes and "one" transfer plasmid containing TKL/TKR and immunoglobulin genes encoding both heavy and light chains, the specification and claims do not provide ***any*** examples for other processes like direct ligation and homologous recombination that would likewise yield a "library" of antibodies upon expression. Therefore, the Examiner contends that Applicants have not provided a "representative" number of examples to show that they were in possession of the full scope of the claims.

With respect to adequate disclosure Applicants are referred to the discussion in *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997; No. 96-1175) regarding disclosure. For adequate disclosure, like enablement, requires *representative examples*, which provide reasonable assurance to one

skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that *applicant had possession of the full scope of the claimed invention.* See *In re Riat* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and University *of California v. Eli Lilly and Co* cited above (for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure.

Here, the general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe that vast majority of methods and vaccinia virus genomes that could be used to produce the claimed libraries, listing examples a few examples of "tri-molecular" recombination is not sufficient to teach the broader genus.

In addition, Applicants specification does not provide any general teaching that would allow a person of skill in the art to extend the "tri-molecular" recombination concept to other areas. For example, the prior art teaches that libraries of polynucleotides that encode potential antigen-specific human immunoglobulins generally cannot be produced using "traditional" methods of homologous recombination with poxviruses like vaccinia (e.g., see specification, page 8, paragraph 20, "Although traditional homologous recombination in poxviruses [e.g., vaccinia] is useful for expression of previously isolated foreign DNA in a poxvirus, the method ***is not conducive to the construction of libraries***, since the overwhelming majority of viruses recovered have not acquired a foreign

DNA insert. Using traditional homologous recombination, the recombination efficiency is in the range of approximately 0.1% or less") (emphasis added). In addition, other attempts to increase the efficiency proved to be unsuccessful and/or unpredictable (e.g., see specification, page 9, paragraph 22, wherein "direct ligation" was shown to be unsatisfactory, "Although large DNA fragments are efficiently cloned into the genome [via direct ligation], proteins encoded by the DNA insert will only be expressed at the low level ... In addition, the DNA will be inserted in both orientations at the NotI site, and therefore might not be expressed at all"). Thus, the prior art teaches that only poxvirus vectors that possess genomes capable of undergoing "tri-molecular" recombination [i.e., the "two" v7.5/tk vaccinia virus genome fragments produced using the NotI/ApaI restriction enzymes] will reliably produce recombinants at an efficiency that is amenable for polynucleotide library construction (e.g., see specification, page 9, paragraph 23, "***poxvirus vectors were previously not used*** to identify previously unknown genes of interest from a complex population of clones, because a high efficiency, high titer-producing method of cloning did not exist for pox viruses ... [***until***] the present inventor developed a method for generating recombinant poxviruses using ***tri-molecular recombination*** [i.e., only vaccinia virus vectors that are amendable to "tri-molecular" recombination will work]"). Consequently, one of skill in the art would reasonably conclude that Applicants were in possession of methods for selecting polynucleotide which encode an antigen-specific human imunoglobuline molecules using only materials and method steps that are required for "tri-

molecular" recombination. Thus, applicants were not in possession of the "full scope" of the claimed invention.

19. Claims 84, 88-97, 99, 103, 107-122 and 127-131 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of selecting polynucleotides which encode an antigen-specific human immunoglobulin molecule via homologous recombination using "two" non-overlapping fragments of the cleaved v7.5/tk or vEL/tk virus genomes produced using NotI/ApaI restriction enzymes and "one" transfer plasmid containing TKL/TKR and a library of human immunoglobulin genes containing both heavy and light genes (i.e. "tri-molecular" recombination process, see specification, page 9, paragraph 24), is not enabled for a method employing any vaccinia virus genome produced via any method. The method is also enabled only when a "helper virus" is used in conjunction with the vaccinia virus vector (e.g., the Fowlpox-virus). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". Some of these factors may include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;

(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) The breadth of the claims and the nature of the invention: The claims are drawn to a broad genus. The scope of these claims include an enormous number of methods using an enormous number of potential viral genomes produced by an unspecified number of methods. Consequently, the nature of the invention cannot be fully determined.

(3 and 5) The state of the prior art and the level of predictability in the art: The prior art teaches that libraries of polynucleotides that encode potential antigen-specific human immunoglobulins generally cannot be produced using "traditional" methods of homologous recombination with poxviruses like vaccinia (e.g., see specification, page 8, paragraph 20, "Although traditional homologous recombination in poxviruses [e.g., vaccinia] is useful for expression of previously isolated foreign DNA in a poxvirus, the method ***is not conducive to the construction of libraries***, since the overwhelming majority of viruses recovered have not acquired a foreign DNA insert. Using traditional homologous recombination, the recombination efficiency is in the range of approximately 0.1% or less") (emphasis added). In addition, other attempts to increase the efficiency proved to be unsuccessful and/or unpredictable (e.g., see specification, page 9, paragraph 22, wherein "direct ligation" was shown to be unsatisfactory, "Although large DNA fragments are efficiently cloned into the genome [via direct

ligation], proteins encoded by the DNA insert will only be expressed at the low level ... In addition, the DNA will be inserted in both orientations at the NotI site, and therefore might not be expressed at all"). Thus, the prior art teaches that only poxvirus vectors that possess genomes capable of undergoing "tri-molecular" recombination [i.e., the "two" v7.5/tk vaccinia virus genome fragments produced using the NotI/ApaI restriction enzymes] will reliably produce recombinants at an efficiency that is amenable for polynucleotide library construction (e.g., see specification, page 9, paragraph 23, "***poxvirus vectors were previously not used*** to identify previously unknown genes of interest from a complex population of clones, because a high efficiency, high titer-producing method of cloning did not exist for pox viruses ... [***until***] the present inventor developed a method for generating recombinant poxviruses using ***tri-molecular recombination*** [i.e., only vaccinia virus vectors that are amendable to "tri-molecular" recombination will work]").

In addition, the prior art indicates that vaccinia virus will not infect mammalian host cells without a helper virus (e.g., see specification, page 7, paragraph 18, "Naked vaccinia virus DNA is not infectious because the virus cannot utilize cellular transcriptional machinery and relies on its own proteins for the synthesis of viral RNA"). In this regard, it is noted that claims which lack critical or essential subject matter, which is necessary to the practice of the invention, but is not included in the claim(s), including essential compound structure, is not enabled by the disclosure. See In re Mayhew, 527 F.2d 1229, 188

USPQ 356 (CCPA 1976); and Ex Part Bhide (Bd Pat. App. & Int.) 42 USPQ2d 1441. Here, Applicants method ***will not work*** without the use of a helper virus.

(4) The level of one of ordinary skill: The level of skill required would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants disclose the use of examples that contain "two" non-overlapping fragments of the v7.5/tk virus genome produced using the NotI and ApaI restriction enzymes and "one" recombinant plasmid containing TKL/TKR and the library of human immunoglobulin genes to produce the vaccinia virus vectors. In addition, all examples employ the use of a "helper" virus like fowlpox virus.

(8) The quantity of experimentation needed to make or use the invention base on the content of the disclosure: As a result of the broad and unpredictable nature of the invention and the lack of specific guidance from the specification, the Examiner contends that the quantity of experimentation needed to make and or use the invention would be great. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 * n.23 (Fed. Cir. 19991). In this case, Applicants have not provided any working examples that would teach this enormous genus that falls within a highly unpredictable art area. Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant

disclosure one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation.

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

22. Claims 84, 88-97, 99, 103, 107-122 and 127-131 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rowlands et al. (WO 93/01296) (Date of Patent is **January 21, 1993**) and Zauderer et al. (WO 00/28016) (Date of Patent is **May 18, 2000**) and Waterhouse et al. (Waterhouse, P.; Griffiths, A.D.; Johnson, K.S.; Winger, G.

"Combinatorial infection and in vivo recombination: a strategy for making large phage antibody repertoires" *Nucleic Acids Research*, **1993**, 21, 9, 2265-2266).

For ***claims 84, 88, 96-97, 113, 117***, Rowlands et al. (see entire document) teach a method for producing antibodies in vaccinia infected cells that reads on the presently claimed invention (e.g., see Rowlands et al., abstract). For example, Rowlands et al. teach **[a-c]** the use of a population of mammalian host cells (e.g., see page 4, paragraph 2; see also paragraph bridging pages 7-8) for introducing and expressing a first/second polynucleotide encoding, through operable association with a transcriptional control region a first/second immunoglobulin polypeptide comprising both heavy/light chain constant/variable regions and a signal peptide for secretion using a vaccinia virus vector (e.g., see claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter"; see also page 2, middle paragraph, "An antibody molecule is composed of two light chains and two heavy chains ... Each heavy chain has at one end a variable domain followed by a number of constant domains, and each light chain has a variable domain at one end and a constant domain at the other end"; see especially page 4, second full paragraph, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be

recovered in functional form"). Rowlands et al. do not explicitly state that a "signal" peptide is being used, but the Examiner contends that this feature is inherent in the method disclosed by Rowlands et al. because the fully functional recombinant antibody would not be "secreted" unless it has such a sequence. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

In addition, Rowlands et al. disclose **[d]** contacting said immunoglobulin molecules or fragments thereof with an antigen and detecting specific antigen-antibody complexes (e.g., see pages 18-19 and Table I wherein the Campath 1H antigen was "contacted" with said immunoglobulin molecules and "detection" was carried out using both T-cell and antigen binding assays). Finally, Rowlands et al. disclose **[e]** recovering the vaccinia virus vectors containing polynucleotides of said first library which encode immunoglobulin subunits polypeptides which, as part of an immunoglobulin molecule, or antigen-specific fragment thereof are specific for said antigen (e.g., see page 5, paragraph 1, step 4, wherein the virus is "harvested" several times [i.e., recovered and/or isolated]).

For ***claim 103***, Rowlands et al. disclose a T7 phage promoter active in cells in which T7 RNA polymerase is expressed (e.g., see page 8, paragraph 2,

"Expression levels of the two chains of the antibody can be enhanced by use of T7 polymerase to amplify the gene under the control of the T7 promoter").

For ***claims 121-122***, Rowlands et al. disclose ELISA (e.g., see page 18, line 7).

The prior art teachings of Rowlands et al. differ from the claimed invention as follows:

For ***claim 84***, Rowlands et al. are deficient in that they do not specifically teach the use of a "library" of first/second polynucleotides.

For ***claims 89-91***, Rowlands et al. do not disclose repetitive steps for "biopanning" a library.

For ***claims 92-95***, Rowlands et al. do not provide "isolating" steps.

For ***claim 99***, Rowlands et al. do not disclose an MOI of 1.

For ***claim 107, 110, 127-131***, Rowlands et al. do not disclose method steps for "tri-molecular" recombination.

For ***claims 108-109, 111-112***, Rowlands et al. do not disclose v7.5/tk or vEL/tk virus genomes with NotI/ApaI restriction sites.

For ***claims 114-116, 118-120***, Rowlands et al. do not disclose the use of virus "pools."

However, Zauderer et al. and Waterhouse et al. teach the following limitations that are deficient in Rowlands et al.:

For ***claim 84***, Zauderer et al. (see entire documents) teach the use of a "library" of polynucleotides in a vaccinia virus vector using the "tri-molecular recombination" approach for screening purposes (e.g., see Zauderer et al., page

52, lines 13-16, "The high yield of viral recombinants in tri-molecular recombination makes it possible, for the first time, to efficiently construct genomic or cDNA libraries in a vaccinia virus derived vector"; see also page 15, paragraph 1; see also page 22, last two paragraphs; see also Example 6 on pages 42-52). In addition, Waterhouse et al. teach that a "library" can be usefully employed to screen for antibodies with high affinity to various antigens including the use of heavy/light chains that are "packaged together" (see Waterhouse et al., page 2265, column 1; see also paragraph bridging pages 2265-2266). The Examiner further notes that Applicants' elected mammalian "HeLa" cells are disclosed also by Zauderer et al. (e.g., see Zauderer et al., page 32, line 2).

For ***claims 89-91***, Zauderer et al. disclose the use of vaccinia virus library vectors that require the use of a helper virus (i.e., are "incapable of producing infectious vaccinia virus") to infect host cells (e.g., see Zauderer et al., paragraph bridging pages 97-98, "Vaccinia virus DNA is not infectious as the virus cannot utilize cellular transcriptional machinery ... Previously ... non-homologous poxvirus fowlpox ... have been utilized as helper virus for packaging"). Zauderer et al. also indicate that the steps for introducing said vectors into host cells, permitting the expression of said vectors, contacting said expressed antibodies with an antigen and recovering said vectors can be repeated as needed to increase the specificity and/or binding affinity (e.g., see page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure").

For ***claims 92-95***, Zauderer et al. disclose "isolating" the polynucleotides contained in the vaccinia virus vectors (e.g., see Zauderer et al., page 52, lines 20-23; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves combining isolated fractions]").

For ***claim 99***, Zauderer et al. disclose, for example an MOI = 1 (e.g., see page 86, line 2).

For ***claims 107, 110, 127-131***, Zauderer et al. disclose "tri-molecular" recombination, which includes, for example, cleavage of v7.5/tk or vEL/tk virus genomes with NotI/ApaI restriction enzymes and "one" transfer plasmid containing TKL/TKR and a library of human immunoglobulin genes containing both heavy and light genes to form vaccinia virus vectors via homologous recombination and method steps for screening and purifying said vectors repeated as many times as are needed to produce the desired products (e.g., see pages 48-52, sections 5.2-5.3; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves combining isolated fractions]"; see also claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter").

For ***claims 108, 111***, Zauderer et al. disclose both v7.5/tk and vEL/tk (e.g., see figure 1).

For ***claims 109, 112***, Zauderer et al. disclose both NotI and ApaI (e.g., see figure 10).

For ***claims 114-116, 118-120***, Zauderer et al. disclose the use of "virus pools" (e.g., see page 51, last paragraph, especially line 27; see also page 58, Table V wherein multiple cycles are disclosed; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves combining isolated fractions]").

It would have been obvious to one skilled in the art at the time the invention was made to make a library of vaccinia virus vectors as taught by Zauderer et al. to express fully functional antibodies as taught by Rowlands et al. for the purpose of screening and/or affinity maturation as taught by Waterhouse et al. because Zauderer et al. explicitly state that their libraries can be efficiently produced using the tri-molecular recombination approach with the vaccinia virus vectors (like the vaccinia virus vectors disclosed by Rowlands et al.) and Waterhouse et al. teach that such a library would be useful in screening and affinity maturation. Thus, one of ordinary skill in the art would have been motivated to make the libraries as taught by Zauderer et al. using the heavy/light chain antibodies as disclosed by Rowlands et al. because Zauderer et al. explicitly state that the their "tri-molecular" approach represents an easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells,

which is a preferred embodiment for Rowlands et al. (e.g., see Zauderer et al., page 22, lines 14-17, "Major advantages of these infectious [vaccinia] viral vectors are ... the ease and efficiency with which recombinants can be introduced mammalian cells"). In addition, Waterhouse et al. teach that "associated" light and heavy chains are a "preferred" embodiment for screening and/or affinity maturation because they can be "simultaneously co-selected" (e.g., see Waterhouse et al., page 2265, paragraph 2), which would encompass the "associated" heavy/light chains described by Rowlands et al. Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Zauderer et al. teach several successful examples of library formation using the same vaccinia virus vectors that are disclosed by Rowlands et al. and Waterhouse et al. teach several successful examples of associated light/heavy chains that can be used for screening and/or antibody maturation, which would encompass the heavy/light chain antibodies disclosed by Rowlands et al.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

23. Claims 84, 88-97, 99, 103, 107-122 and 127-131 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-84 of U.S. Patent Application Pub. No. 2003/0104402 A1 (referred to herein as '402) in view of Rowlands et al. (WO 93/01296) (Date of Patent is **January 21, 1993**).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examiner application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1986).

Here, claims 1-84 of U.S. Patent No. '402 recite a method for selecting polynucleotides which encode immunoglobulin molecules which is essentially the same as that disclosed by claims 84, 88-97, 99, 103, 107-122 and 127-131 in the present application (e.g., both methods disclose eukaryotic host cells, a first and second library of polynucleotides encoding immunglobulin light/heavy chain constant/variable regions, permitting expression of said immunoglobulin molecules, contacting the molecules with an antigen, recovering the polynucleotides that encode for immunoglobulins that bind to said antigens, etc).

The method of claims '402 differ from the present application in that they claim "intracellular" as opposed to "extracellular" expression.

However, Rowlands et al. teach the use of a population of mammalian host cells (e.g., see page 4, paragraph 2; see also paragraph bridging pages 7-8) for introducing and expressing a first/second polynucleotide encoding, through operable association with a transcriptional control region a first/second immunoglobulin polypeptide comprising both heavy/light chain constant/variable regions and a signal peptide for secretion using a vaccinia virus vector i.e., "extracellular" expression (e.g., see claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter"; see also page 2, middle paragraph, "An antibody molecule is composed of two light chains and two heavy chains ... Each heavy chain has at one end a variable domain followed by a number of constant domains, and each light chain has a variable domain at one end and a constant domain at the other end"; see especially page 4, second full paragraph, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form"). Rowlands et al. do not explicitly state that a "signal" peptide is being used, but the Examiner contends that this feature is inherent in the method disclosed by Rowlands et al. because the fully functional recombinant antibody

would not be "secreted" unless it has such a sequence i.e., Rowlands et al. teach "extracellular" expression. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Thus, it would have been obvious to modify the method of claims 1-84 of U.S. Patent Pub. No. '402 such that "extracellular" expression was performed instead of "intracellular" expression because Rowlands et al. teach that "extracellular" expression may be obtained within Applicants' preferred vaccinia virus vector. One having ordinary skill in the art would have been motivated to make such a modification because Rowlands et al. teach that their "extracellular" expression is particularly well suited for genes of mammalian origin (e.g., see page 4, first full paragraph), which is a preferred embodiment of the '402 patent application (e.g., see claim 26 of '402). In addition, Rowlands et al. teach that their "extracellular" expression techniques are advantageous "particularly in terms of versatility and speed [because] ... [the] virus will infect a wide range of cells [and] ... [thus] Cell lines suitable for production of a recombinant antibody can thus be derived conveniently and quickly. (e.g., see Rowlands et al., paragraph bridging pages 9-10). Finally, Rowland et al. teach that "extracellular" screening

can be useful in tumor diagnosis and/or analysis (e.g., see page 9, lines 1-4; see also examples wherein Campath antigen is used).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Contact Information

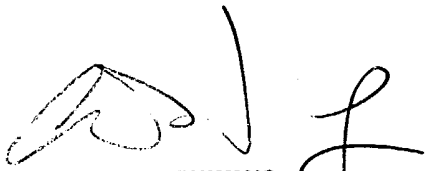
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
August 17, 2004



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